

Autoimmunity

Introduction

The immune system must balance **tolerance** (not activating an immune response to self-antigens) and **immunity** (activating the immune response to foreign antigens). Failure of immunity (too much tolerance) prevents the immune system from reacting to self-antigens, but leads to pathogens with similar-to-self antigens going unopposed. Failure of tolerance (too much immunity) means that while many foreign antigens will be identified and fought, too much activation may result in self-antigens activating an immune response against tissue that is supposed to be in us. Failure of immunity is covered in the final lesson (#15 *Immunodeficiency*); here we discuss the **failure of tolerance**.

Because the innate immune system responds to nonspecific markers as well as to specific ones, and has the same response to both (usually phagocytosis), the innate immune system can't be the cause of autoimmunity. See the phagocytes, complement, and granulocytes just as the grunts. They only do one thing—attack. They don't have good mechanisms for defining whom they should attack; they just do. Without the adaptive immune system, PRRs and PAMPs are the only weapons the innate immune system has. With the adaptive immune system, antibodies tag targets for phagocytosis and cytokines supercharge the phagocytes to do what they do. What that means is that while the cells of the innate immune system will do the destroying, they only destroy tissue marked by the adaptive immune system. That means autoimmunity may be exacted by leukocytes of all kinds, but the pathogenesis **lies squarely and only with the lymphocytes**. It is those cells we will explore.

Because the adaptive immune system **has memory** and because it's the responsibility of the adaptive immune system to release antibodies and cytokines, the **pathogenesis of autoimmunity must be a result of a failure of the adaptive immune system**. When antibodies and cytokines tell the innate immune system to kill something, the innate immune system kills it. It's the responsibility of the adaptive immune system, of the lymphocytes, to determine what the innate immune system should kill. So we'll focus on lymphocytes—B cells and T cells—only.

Physiology of Tolerance

There is both central tolerance and peripheral tolerance. Should a lymphocyte make it through both, the **memory cell will never be tested again**, having passed two separate mechanisms. Therefore, the physiology of tolerance must ensure that no activated lymphocyte reacts to self-antigens. **Central tolerance** occurs in the **primary lymphoid organs** during **maturation**. Central tolerance ensures that “*if you bind, you die*.” On the other hand, **peripheral tolerance** occurs in the **secondary lymphoid organs**, during **activation**. Peripheral tolerance ensures that “*naive cells ask permission from veteran cells*.”

If a self-reacting lymphocyte makes it to memory, there's no way of deleting or inactivating it. Autoimmunity, then, results when a lymphocyte reacts to self-antigen and is then stored in memory. This also implies that once autoimmune disease is present, it can only be controlled, and never reversed (99% true).

B-Cell Tolerance

B cells mature in the bone marrow, where random VDJ-heavy-chain and VD-light-chain rearrangements were the mechanism by which we could create a near-limitless permutation of antibodies, so we could develop an adaptive immune system to any antigen. Because B cells mature in the bone marrow, they develop devoid of foreign antigens to guide them. Because there's so much random variation of the antigen-binding domain (Fab), the bone marrow must first ensure that the random variation didn't create a self-sensing immunoglobulin. Before the **mature naive B cell** is released from the marrow, it's assessed for tolerance. **If the immunoglobulin binds self**, the B cell is killed, induced to apoptosis, eliminating the possibility of proliferation. The cell line is snuffed out. This is **clonal deletion**.

B cells sent from the bone marrow leave on probation. They express IgD. This is both their ticket to ride, an entry fee required to get into the secondary lymphoid organ, and the fail-safe kill-switch. In the secondary lymphoid organs, when the B cell identifies an antigen with its IgM immunoglobulin acting as a receptor, that antigen is internalized, degraded, and presented via MHC-2. The **mature naive B cell** shows the antigen it found to the neighboring **veteran T-helper cell**. If the vet thinks the naive B cell has done well, it sends cytokines as a **costimulatory signal** that induces isotype switching (CD40), proliferation, and splicing out of the IgD probationary card. If the mature T cell disagrees with the B cell, that B cell doesn't get the isotype switching or proliferation signal, and its IgM is taken away, leaving only the probationary IgD immunoglobulin. This cell becomes impotent, will never proliferate, and eventually will just die. This is **clonal anergy**.

Looking at the B cell, we see that **clonal deletion** is the mechanism of **central tolerance** and is in response to **self-antigen binding**, while **clonal anergy** is the mechanism of **peripheral tolerance** and is in the **absence of costimulation**.

T-Cell Tolerance

T cells do something similar—clonal deletion in the thymus, clonal anergy in the secondary lymphoid tissue. The mechanism is a little different.

T-cell central tolerance occurs in the thymus. Positive selection ensures that the TCR works at all. A defective TCR can't result in autoimmunity, but the cell line is deleted just the same. Failure to bind during positive selection results in clonal deletion. But **negative selection** is about self-recognition. If a TCR binds to self-antigen during negative selection, it's deemed intolerant of self, and the cell line is removed; that T cell is induced to apoptosis, and thus **clonal deletion**. Binding self results in death.

T-cell peripheral tolerance follows the same theme—an immature T cell asks a mature APC for costimulation. While in B cell activation the naive B cell presents the antigen to a mature T cell to get growth cytokines, T cell activation involves the mature APC to send the growth cytokines to the immature T cell. It's important to note that cytokines pass from mature to immature cell, not from T cell or from B cell. In addition, many of the mechanisms of activation are the same. The APC has internalized a pathogen (MHC-2) or self-antigen (MHC-1), and is presenting it to a T cell. The T cell uses its TCR to make the connection, stabilized by CD3. B7 on the APC acts as a ligand for CD28 on the T cell, and “another signal” is the third link. The “another signal” was CD40-CD40 ligand in activation of the naive B cell. The T cell “another signal” exists, but you shouldn't learn it, so it's not named here. When the mature cell makes all the right connections, growth cytokines are released. Without those growth cytokines, the TCR is inactivated and that immature T cell undergoes **clonal anergy**.

Central tolerance is deletion (negative selection), and **peripheral tolerance is anergy** (failure of growth cytokines).

How Self-Antigens Get Recognized as Non-Self

Since there must be self-antigen recognition stored in memory to have autoimmune disease, there must be something that happens to escape the safety mechanisms of tolerance and anergy. For autoimmune disease to exist, some lymphocyte had to get permission to identify self as non-self, and no lymphocyte is supposed to be allowed to do that.

But it happens. Something sets it off. That something is the **primary event**. Many people suffer from a primary event and don't develop autoimmune disease. Which means that the primary event is not enough. When you take someone with the **genetic predisposition** and they suffer a primary event, they develop autoimmune disease. The primary event can lead to alteration of self-antigen, release of a sequestered antigen, or mimicry of a foreign antigen. Genetic predisposition is not well understood, but HLA haplotypes are implicated and have become a hot topic in medicine. HLA is what we call MHC in humans.

Alteration of host antigens can occur through infection (viruses), inflammation, or more importantly, by **complexing with a drug**. Drug-induced autoimmune disease is caused by adding a drug. The antibodies are against the drug, but the antibodies still cause autoimmune disease. Hydralazine-induced lupus is caused by antibodies to the hydralazine. The antibody-drug complex provokes the symptoms of the disease. Remove hydralazine, remove antibodies, remove the disease.

Sequestration occurs in body parts like the eye, testicles, and thymus. Tissue that normally has no exposure to the immune system, when exposed (as in trauma), can suddenly have antibodies made against it. 70% of vasectomy patients have antibodies against sperm. Sperm are foreign haploid cells that are very dissimilar to the host male. They are just usually kept away from the immune system, sequestered in the reproductive system with a tight blood-tissue barrier.

Mimicry is thought to be the primary way in which autoimmune disease occurs. Some infectious illness happens. Antibodies are made. **Somatic hypermutation** occurs. The somatic hypermutation is specific to the antigen. But what happens when the antigen resembles self-antigens? In its nonspecific, low-affinity IgM state, the B cell passed the test; IgM lacked the affinity for clonal deletion in the marrow. That same IgM receptor binds the antigen. That same IgM receptor undergoes somatic hypermutation, getting more like the antigen. The IgG that gets made after that process has high affinity for the antigen. But it now has higher affinity for the self-antigen. And the constant presence of self-antigen only stimulates the development of more antibody. And because it underwent somatic hypermutation, it means that it passed the bone marrow (no clonal deletion) and it passed activation (no clonal anergy), so now it has an antibody against self, without a means of turning it off.

We've been discussing autoimmune disease as antibody-mediated, but it doesn't have to be. It's just easier to grasp when it's related to antibodies.

CD8+ HLA-CLASS 1 HLA-A,B,C	CD4+ HLA-Class 2 HLA-DR, DQ
Ankylosing spondylitis = HLA*B27	Rheumatoid arthritis, IDDM = DR4
	Lupus, multiple sclerosis = DR2
	Celiac = DQ2, DQ8

Table 14.1: Genetic Predisposition

You will NOT use HLA-haplotypes as diagnostic tools. However, these are the very high-yield examples of Haplotype association to disease.

Genetic Predispositions

Do NOT attempt to use HLA haplotypes to infer the mechanism of autoimmunity or the type of hypersensitivity reaction caused by the diagnosis. Learn the mechanism of autoimmunity when you learn the diseases. But commit table 14.1 to memory, as they are highly tested. They'll serve you no clinical utility of any kind.

Specific Examples

Rather than teach autoimmune disease under the category of "autoimmune disease," we prefer to allot the diseases of autoimmunity to the organs they affect. For example, lupus and rheumatoid arthritis are found in MSK, Grave's disease in Endocrine, and pernicious anemia in GI.

We've chosen commonly tested diseases to illustrate how a person starts without the autoimmune disease, then subsequently develops one, and we've chosen a variety of diseases to illustrate various hypersensitivity reactions that arise from those diseases. These are brief forays, and these diseases should be more closely attended to, in more detail, in their respective sections.

Type 1 diabetes is autoimmune destruction of the insulin-producing β cells of pancreatic islets. This means the exocrine and endocrine function of the pancreas remains entirely intact except for insulin. A **type 4 T-cell-mediated hypersensitivity**, T cells destroy β cells, and insulin can't be made. This normally develops in **young children**. The child develops normally, then at some age between birth and 18 years of age, "something happens" and suddenly the insulin disappears. The presentation is sudden and abrupt, without progressive symptoms. The glucose is elevated, overwhelming the T_{max} of glucose resorption in the kidney, leading to dehydration. The patient presents in DKA with coma, or with **polyphagia, polydipsia, and polyuria**. There is no management of the disorder except to provide exogenous (injectable) insulin.

Systemic lupus erythematosus is an autoimmune disease against soluble circulating antigens. These antigens are soluble, and so are everywhere. **Antibodies** are made against the antigen. These antigen-antibody complexes then deposit throughout the body. It's a **type 3 antibody-antigen-complex deposition hypersensitivity reaction**. The complexes deposit in the skin (ultraviolet light sensitivity, **malar rash**), joints (**joint pain**), and kidneys (**renal failure**). The diagnosis is facilitated by assessing for the circulating antibodies: antinuclear antibodies (ANA), double-stranded DNA antibodies (dsDNA), Smith antibodies (Smith), and, in the case of drug-induced lupus, histone antibodies (antihistone).

Myasthenia gravis is a **noncytotoxic antibody-mediated (type 2, noncytotoxic)** autoimmune disease. Antibodies are made against the postsynaptic ACh receptors at the muscle endplate. The antibodies bind to these receptors, competitively inhibiting the receptor. On depolarization of the presynaptic cell, ACh is released, overcoming the antibodies, allowing contraction. On repeated contraction, the ACh vesicles deplete, and the concentration of ACh in the endplate goes down, allowing the antibodies to dominate. Therefore, the disease is characterized by **reduced force of contraction on repeated contractions**.

Streptococcal glomerulonephritis is a **cytotoxic antibody mediated (type 2, cytotoxic)** autoimmune disease. Antibodies are made against the strep bacteria during a skin infection or throat infection. Cross-reactivity of the antibody against the bacteria and the kidneys leads to **autoimmune destruction of the kidneys**.